With response to the Examiner's objection to the use of the term "exhibits a preference for concentration" in Claims 12 and 13, Applicants have amended these claims to recite -- substantially concentrates -- . This is clearly supported in the specification at page 7, lns. 1-5.

In Claims 16 and 23, the Examiner objects to the use of at and near. The amendment to Claims 16 and 23 of "proximate to or into" tissue of cancer or tumors is supported by the specification at page 7, lns. 12-27 and was accepted in the parent application.

With regard to "biologically targeting" and "chemically targeting" in claims dependent on Claim 12, "chemical targeting" pertains to the radiosensitizer agent targeting the diseased tissue based upon physicochemical affinity between the agent and the target (i.e., diseased tissue). This targeting can be enhanced by, for example, functional derivatization at positions R^1 or R^2 by attachment of certain chemical moieties, such as those disclosed at p. 9, lines 8-13, so as to change the partitioning of the agent onto or into certain tissues, and thereby effect the chemical targeting. This is disclosed, for example, at p. 7, lines 14-17 of the present application and is clearly understandable by those skilled in the art. Further details are disclosed, for example, at p. 9, lines 14-16.

Biological targeting is disclosed, for example, at p. 9, lines 3-13 of the present application. As defined therein, and as understood by those skilled in the art, such targeting pertains to agent targeting based on biological affinity (such as antigen-antibody, receptor-target, or nucleic acid hybridization) between the radiosensitizer agent the target (i.e. diseased tissue). This targeting can be enhanced by, for example, functional derivatization at positions R^1 or R^2 with certain biological moieties, such as those disclosed at p. 9, lines 8-13, including for example nucleic acids, antibodies, and haptens, so as to enhance the affinity of the radiosensitizer agent for certain tissues, and thereby effect the biological targeting.

Applicants have now amended the claims to clarify the difference regarding "biological targeting" in Claim 14 and "chemical targeting" in Claim 15.

Applicants disagree with the Examiner's assertion that the term "biologically sensitive structures" is indefinite. This terminology is clearly defined at page 6, lns. 23-24 of the present application and is know to those skilled in the art. Hence, it is requested that this objection be withdrawn. The Examiner approved of similar amendments in the parent application.

Further, in accordance with the Examiner's request in the parent application, the claims have been amended to recite "radiosensitizer agent", though it is not believed that such amendment is necessary to provide an antecedent basis for "said agent" or "the agent" in these claims.

The Examiner also rejected Claims 1-30 and 51-52 under 35 USC §112 as being enabling for the treatment of diseased tissue such as cancer and tumor cell tissues, but not for treatment of any diseased tissue such as parasitized and infected muscle tissue. Accordingly, Applicants have amended the claims to recite treatment "A radiosensitizer agent for treatment of cancer and tumors" and no longer recite "diseased tissue".

Applicants are also adding new dependent claims to further claim the subject matter of the present application. It is not believed that any new matter is being added in these claims and that they are allowable for the reasons given herein. Please charge our deposit account 50/1039 for any fee due for these additional claims.

Accordingly, it is respectfully submitted that the amended and new claims are not indefinite and should be allowed.

The §102 Rejections

I. First §102 Rejection

The Examiner also rejects Claims 1-3, 5-8, 10, 12-13, 15-16, 23, 28-30 and 51 under 35 USC §102 as being anticipated by Serafini et al. This rejection is respectfully traversed.

The present invention, as recited in independent Claims 1 and 12 and those claims dependent thereon, is directed to a radiosensitizer agent for treatment of cancer and tumors using radiosensitization or ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene (Claims 1 and 12) wherein said radiosensitizer agent substantially concentrates in said cancer or tumors (Claim 12). Dependent Claims 2, 19, 26 and 28 specify the halogenated xanthene is Rose Bengal.

None of the cited references disclose or suggest the agent of these claims.

Serafini et al.

The relevance of Serafini et al. (J. Nucl. Med., 1975), if any, appears to be that it concerns a diagnostic use for Rose Bengal in scintographic imaging. This article describes the use of certain radioactive forms of Rose Bengal in the medical evaluation of liver function. In the diagnostic test, a radioactive form of the compound (radiolabelled with iodine-131 or, as taught by Serafini, with iodine-123) is administered to the patient as an intravenous bolus. The subsequent distribution of the diagnostic agent throughout certain organs of the patient's body is then determined by detecting the emissions from the radioactive decay of the radioactive iodine contained in this radiolabelled Rose Bengal[1]. Serafini describes use of a radiation detection system for detecting the natural radioactive

[1]In the abstract, Serafini refers to "overall reduction in ... radiation exposure" as a result of substitution of iodine-123 labeled Rose Bengal for the conventional iodine-131 labeled form. This is described further in the DISCUSSION section, pp. 631 and 632: wherein it is explained that the

decay of the iodine using a "scintillation camera." Serafini is thus concerned with an application in nuclear medicine where the natural radioactivity of a substance is put to use. The substance, in Serafini's case Iodine-123-Rose Bengal, emits radiation which Serafini reports on for imaging purposes. As seems appropriate, this article appears in a journal directed to nuclear medicine.

Unlike the radiosensitizer agent claimed in independent Claims 1 and 12 of the present, which use radiosensitization or ionizing radiation for treatment of cancers or tumors, in Serafini a radiosensitizer agent is not disclosed or suggested since no exogenous radiation is therapeutically, diagnostically or otherwise applied to the tissue containing the Rose Bengal. (Any radiation emanating from I-123 or I-131 that hits the tissue as a result of the radioactive decay of the imaging agent is not regarded as "ionizing radiation" or "radiosensitization" within the meaning of these two independent claims.) As a result, there is no suggestion in Serafini of using Rose Bengal or any other halogenated xanthene (Serafini does not disclose the use of any other halogenated xanthene) as a radiosensitizer agent as required in the claims of the present application.

Additionally, Applicants find no suggestion of any therapeutic modality in Serafini, unlike independent Claims 1 and 12 of the present application which is specifically directed to a radiosensitizer agent for treatment of cancer and tumors using radiosensitization or ionizing radiation. As a result, Serafini appears to have almost no relevance to the present invention.

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radioactive half-life of iodine-123 is 13 hours, while the radioactive half-life of iodine-131 is 8 days. Hence, for similar doses of radioactive material, the patient would be subjected to a markedly shorter period of harmful radioactive emission from the iodine-123 compound relative to that from the iodine-131 compound. Clearly, this reduction in exposure is not directed to the applied radiation involved in the present invention.

II. Second §102 Rejection

The Examiner also rejects Claims 1-3, 5-10, 12-13, 15-16, 23, 28-30 and 51 under 35 USC §102 as being anticipated by Neckers. This rejection is also respectfully traversed.

Neckers

The Examiner cites Neckers for teaching the properties of Rose Bengal and its derivatives. Neckers merely describes the many fundamental chemical and physical properties of the halogenated xanthenes, particularly Rose Bengal. There is, however, no teaching or suggestion of properties related to the interaction of such agents with ionizing radiation or the use of such agents upon interaction with such ionizing radiation for treatment of cancer or tumors, as required in the claims of the present application. In fact, Applicants are unaware of any prior art relating to such interactions. Rather, the work of Neckers only describes the interaction of visible light (i.e., absorbance and subsequent results of such interaction) with such agents.

It is respectfully submitted that one of ordinary skill in the art would not be led to using these agents as radiosensitizers based on prior art, such as that of Neckers, pertaining to the photochemical use of such agents with visible light activation. The fundamental physics of activation with visible light and with ionizing radiation are completely different. More specifically, visible light activation of the halogenated xanthenes results in photocatalytic conversion of triplet oxygen into cytotoxic singlet oxygen, while activation of any radiodense material, such as the halogen atoms contained in the halogenated xanthenes, with ionizing radiation results in cell necrosis from spontaneous re-emission of such activating energy from such radiodense materials at lower, more cytotoxic energies. Further, since key features characterizing the interaction of visible light with the halogenated xanthenes vary with the overall molecular structure of such agents (as evidenced by variations in optical spectroscopic properties, such as absorbance maxima and excited state lifetime, with changes

in location of halogen substitution, as clearly taught throughout Neckers), while the key features characterizing the interaction of ionizing radiation with such agents is affected only by absolute halogen content (and not by their location within the molecule), then the conceptual role of the agent with regard to these two activation means is fundamentally different (i.e., with visible light activation, the halogens serve to modify the photochemical and photophysical properties of the molecule, while upon activation with ionizing radiation, the halogenated xanthene molecule serves as a vehicle for concentration and delivery of the active halogens).

Accordingly, for the above-stated reasons, Neckers does not disclose or suggest the radiosensitizer agent of the claims of the present application, and those claims are clearly not anticipated by Neckers but are patentable thereover.

III. Third §102 Rejection

The Examiner also rejects Claims 12-17, 21-24, 28-29 and 52 under 35 USC §102 as being anticipated by Norman et al (1991). This rejection is respectfully traversed.

Applicants have now amended independent Claim 12 to recite that the radiosensitizer agent comprises a halogenated xanthene, and therefore, all claims pending herein include a radiosensitizer agent comprising a halogenated xanthene. As Norman clearly does not disclose a radiosensitizer agent that includes a halogenated xanthene, Norman cannot anticipate the claims of the present application. Accordingly, this rejection should now be withdrawn.

§103 Rejections

I. First §103 Rejection

The Examiner also rejects Claims 18 and 25 under 35 USC §103 as being unpatentable over Norman et al. in view of Khaw et al. This rejection is respectfully traversed.

As explained above, Norman does not disclose or suggest a radiosensitizer agent comprising a halogenated xanthene. Neither does Khaw.

Instead, Khaw et al. discloses methods of manufacture and use of immunoliposomes (i.e., liposomes doped on their outside surface with an immunoactive moiety, such as an antibody). Such immunoliposomes are purported to provide means for targeted delivery of their contents to various immunologic targets (such as certain cancer cells) (see, e.g. col. 6, lns. 44-50). Use of such immunoliposomal delivery means is taught for use with therapeutic radioactive iodine (see col. 11, lns. 37-46) and for various "radiopaque" materials (see col. 11, lns 53-64). Specific examples of such use with contrast agents is given in Table I: Additional uses with radiosensitizing compounds is disclosed at col. 13, lns. 62-65. This is further discussed at col. 16, lns. 9-34 and lns. 52-60, and at col. 17, lns 13-16.

Notably, Khaw et al. teaches that such delivery is based primarily on action of a specific affinity reagent (i.e., the immunoactive moiety) with specific intracellular antigens, as taught at col. 3, lns. 14-21. This fundamental concept is markedly different than the teachings of the present invention, which discloses new radiosensitizer agents (i.e. halogenated xanthenes) that exhibit intrinsic targeting for certain types of cells and tissues along with certain structural components of such cells and tissues (see, e.g. p. 6, ln. 12 - p. 7, ln. 23, of the present application). As a result, Khaw et al. teaches away from the subject matter of the present invention by requiring use of specific immunologic delivery means and liposomal packaging for successful transport and delivery of

radiocontrast or radiosensitizer agents to diseased tissue. In contrast, in the present invention, such complex adjuvants are not required, but instead simple adjuvants (i.e. simple liposomal formulations, rather than Khaw's more complex immunoliposomes) can be used in the formulation and optimization of such agents for certain physical targeting purposes (see e.g. p. 7, lns. 17-21 of the present application). Thus, while Khaw ***requires*** immunoliposomes for successful targeting and delivery of the liposomal contents, the present application does not have such a requirement.

Further, Khaw does not disclose or suggest the use of halogenated xanthenes as radiosensitizer agents.

Hence, even when combined, these two references fail to disclose or suggest the radiosensitizer agent comprising a halogenated xanthene of the claims of the present application. Therefore, the claims are patentable over these references.

II. Second §103 Rejection

The Examiner also rejects Claims 4, 11, 14, 17-22 and 24-27 under 35 USC §103 as being unpatentable over Serafini or Neckers in view of Khaw et al. This rejection is respectfully traversed

As explained above, neither Serafini, Neckers nor Khaw disclose or suggest the radiosensitizer of the claims of the present application. In particular, even when combined, these references fail to disclose a radiosensitizer agent for treatment of cancer and tumors using radiosensitization or ionizing radiation, said radiosensitizer agent comprising a halogenated xanthene. Accordingly, for the reasons stated herein, the claims are patentable over these references, even when combined.

Conclusion

For the above-stated reasons, it is respectfully submitted that the claims of the present application are neither disclosed nor suggested by the cited references and are patentable thereover. Accordingly, it is requested that the claims be passed to allowance.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

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